



Penicillin-allergic patients: Use of cephalosporins, carbapenems, and monobactams

Author

Roland Solensky, MD

Section Editor

N Franklin Adkinson, Jr, MD

Deputy Editor

Anna M Feldweg, MD

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INTRODUCTION — Penicillin allergy is reported by up to 10 percent of people. A common clinical question is whether these individuals can safely receive structurally-related antibiotics, such as cephalosporins, carbapenems, and monobactams.

This topic will discuss cross-reactivity between penicillins and structurally-related antibiotics in patients with type I, IgE-mediated allergy to penicillins. Penicillin allergy, skin testing, graded challenge (test dosing) and desensitization are reviewed separately. (See "[Allergy to penicillins](#)".)

Antigenic components of penicillins — In order to understand the possible cross reactivity among penicillins, cephalosporins, carbapenems and monobactams, it is helpful to review the potential allergens in penicillins. Patients with IgE-mediated allergy to penicillins may be reactive to the beta-lactam ring structure that is common to all penicillins, or to the R-group side chains that distinguish different penicillins from one another. In the United States, most penicillin allergic patients are sensitive to the beta-lactam core. In contrast, in southern Europe where [amoxicillin](#) constitutes 90 percent of antibiotic use in some countries, up to one third of patients are said to react to the R group side chain. (See "[Allergy to penicillins](#)".)

- A beta-lactam structure is also found in cephalosporins, carbapenems, and monobactams ([figure 1](#)).
- The aminopenicillins [amoxicillin](#) and [ampicillin](#) each have R-group side chains that are identical to the side chains of certain cephalosporins ([table 1](#)).

Multiple drug allergy syndrome — Multiple drug allergy syndrome is a term used to describe individuals who develop allergic reactions (either IgE- or non-IgE-

mediated) to two or more non-crossreacting medications. It identifies a subset of individuals with an increased propensity for reacting to medications, for varied reasons that are only partly understood.

In studies of patients with allergies to structurally related antibiotics, the concept of multiple drug allergy syndrome should be considered as a possible confounding factor [1]. This was illustrated in several large studies, which yielded unexpected results attributable to multiple drug allergy syndrome:

- In patients with a previous documented penicillin allergic-like event, the relative risk for an allergic-like event was higher not only for cephalosporins (10.1, confidence interval [CI] = 7.4 to 13.8), but also for the structurally distinct sulfonamides (7.2, CI = 3.8 to 13.5) [2].
- Another study evaluated the incidence of allergic reactions to antibiotics in patients who had previously undergone penicillin skin testing [3]. Among these penicillin skin test-positive patients, allergic reactions during the first post-testing antibiotic treatment occurred more frequently with non-beta-lactam antibiotics (10.8 percent) than with cephalosporins (2.4 percent) [3].

Thus, multiple drug allergy may confound studies of potential cross-reactivity unless appropriate controls are included. Specifically, patients who are allergic to one drug and are challenged with a potentially related drug should also be challenged with an unrelated drug.

CEPHALOSPORINS — There are two sources of structural similarity between the penicillins and the cephalosporins, as mentioned previously: the beta-lactam ring common to all penicillins and cephalosporins, and R group side chains that are shared by specific drugs (figure 1). Based on limited data from Spain, the R group side chains are believed to be most important in predicting cross-reactivity between aminopenicillins and cephalosporins [4-6].

Amoxicillin and ampicillin each share R groups side chains with several cephalosporins (table 1). As an example, amoxicillin and cefadroxil have identical side chains, and patients with IgE directed against the R-group would potentially react to these two drugs, but not to penicillin itself.

In vitro and skin testing studies with penicillin and cephalosporins showed a high degree of immunologic cross-reactivity [7-11], although this does not consistently translate into clinical cross-sensitivity, as described below.

Limitations of clinical cross-reactivity studies — Most studies of clinical cross reactivity between penicillins and cephalosporins have been limited by the following issues:

- Most cephalosporin challenges in the available studies were carried out in open fashion, rather than single- or double-blinded.
- All studies are lacking the control groups needed to identify patients with multiple drug allergy syndrome, such as penicillin skin test-positive patients challenged with a non-beta-lactam antibiotic, or patients allergic to a non-beta-lactam antibiotic challenged with cephalosporins [\[12,13\]](#). (See ['Multiple drug allergy syndrome'](#) above.)

Risk of administration in patients with reported penicillin

reactions — Among patients who report penicillin reactions (but do not undergo confirmatory testing), between 0.17 and 8.4 percent will react if given a cephalosporin. This estimate is based upon retrospective studies in which patients with a history of penicillin allergy were treated with cephalosporins WITHOUT preceding penicillin allergy testing (skin testing or in vitro testing) ([table 2](#)) [\[14-18\]](#).

These studies have some additional limitations. Among the five leading reports, two were from the 1970s, and cephalosporins produced prior to 1980 are known to have been contaminated with trace amounts of penicillin [\[19\]](#). In addition, these reports provided no information on the nature of the cephalosporin reactions. In the best-designed studies, there were two reactions to cephalosporins that were very questionable [\[16,17\]](#). One of the reactions was worsening of eczema after several days of cephalosporin treatment and the other consisted of documentation in the anesthesia record of preoperative administration of [hydrocortisone](#) and [diphenhydramine](#) in a patient on chronic glucocorticoid treatment.

In addition to the specific issues discussed above, there are some general design limitations:

- A significant subset of the patients in these studies were likely not allergic to penicillin at the time they were treated with cephalosporins, since large studies have shown that only about 10 to 15 percent of all patients who report a penicillin reaction in the past are found to have IgE-mediated penicillin allergy upon definitive evaluation [\[20-23\]](#). This is reviewed elsewhere. (See ["Allergy to penicillins", section on 'Introduction'](#).)
- There was presumably a selection bias in these real world studies in deciding which patients (ie, probably not the ones with recent or severe penicillin reaction histories) to treat with cephalosporins instead of non-beta-lactam antibiotics.

For all of these reasons, these studies are not definitive regarding the frequency of reactions to cephalosporins in penicillin-allergic subjects.

Risk of administration in patients with confirmed penicillin

allergy — Penicillin-cephalosporin cross-reactivity studies that confirmed penicillin allergy by skin testing are superior in design compared to those that diagnosed penicillin allergy by history alone. Another group of studies evaluated patients with positive penicillin skin tests (to PPL, [penicillin G](#) and/or MDM) who were challenged with cephalosporins, and found an overall reaction rate of 3.4 percent ([table 3](#)). If this analysis is limited to studies published after 1980 (when cephalosporins were no longer contaminated with penicillin), the reaction rate is reduced to 2 percent. Thus, approximately 2 percent of patients with skin-test proven sensitivity to penicillin can be expected to react to cephalosporins.

In the studies above, some investigators additionally performed cephalosporin skin testing (on penicillin test-positive patients) prior to cephalosporin administration, and administered cephalosporins only if those tests were negative (since ethical concerns prevented cephalosporin challenges in patients with positive cephalosporin skin tests) [[4,24-26](#)]. Because test-positive patients were not challenged with cephalosporins, the positive predictive value of cephalosporin skin testing could not be assessed.

The approach outlined in this topic does not involve skin testing to cephalosporins. However, if desired, solutions for this purpose can be prepared from injectable therapeutic preparations. These should be freshly prepared on the day of use.

- A concentration of 2 mg/mL (in normal saline) was shown to be nonirritating (for both epicutaneous and intradermal application) in a group of 40 nonallergic control subjects for several injectable cephalosporins [[27](#)].
- Another study in 25 healthy volunteers found that 10-fold dilutions of commercially available IV preparations of cephalosporins were nonirritating for intradermal skin testing [[28](#)]. These concentrations translate to 10 mg/mL for [ceftriaxone](#), [cefuroxime](#), [ceftazidime](#), and [cefotaxime](#) and 33 mg/mL for [cefazolin](#).

Algorithm for management — The approach to administration of cephalosporins to patients with a history of penicillin allergy can be divided into scenarios when penicillin skin testing is or is not available ([algorithm 1](#)). Penicillin skin testing reagents are currently available commercially in the United States and many other parts of the world, although there have been periods of time in which they were not

manufactured. The protocol for penicillin skin testing is discussed elsewhere. (See ["Allergy to penicillins", section on 'Penicillin skin testing'.](#))

Penicillin skin testing is available — The results of penicillin skin testing can be used to guide management, as follows:

- If penicillin skin testing is performed and is negative, patients may safely receive cephalosporins ([algorithm 1](#)) ([table 1](#)).
- If penicillin skin testing is positive, then about 2 percent of these patients can be anticipated to react to cephalosporins. Without precautions, some of these reactions could be severe or life-threatening. Therefore, the options for management are:

Administer an unrelated antibiotic (neither a penicillin nor a cephalosporin).

Administer a cephalosporin using a graded challenge. This is only necessary the first time a cephalosporin is given after testing and evaluation. (See ['Graded challenge'](#) below.)

Administer a cephalosporin using a rapid desensitization procedure. This is the most conservative approach, and would be reserved for patients who were either at high risk for a recurrent reaction based on clinical characteristics, or who had comorbidities that would make them less likely to be able to withstand a recurrent reaction. Desensitization techniques are reviewed separately.

(See ["Allergy to penicillins", section on 'Desensitization'.](#))

Penicillin skin testing is not available — If skin testing is not available, the clinician must estimate the chances of a serious IgE-mediated reaction to a cephalosporin based on the clinical history and time elapsed since the penicillin reaction. Based on large studies in which skin testing was performed, only 10 to 15 percent of patients reporting penicillin reactions will have positive penicillin skin tests. Of these, most (99 percent based upon the best-designed studies above [[16,17](#)]) will tolerate a cephalosporin, especially one with a side chain group that is dissimilar to the culprit penicillin. Thus, we suggest the following approach:

- The patient is at lower risk for reacting to a cephalosporin if the reaction to penicillin occurred more than 10 years ago, and the symptoms involved were not suggestive of an IgE-mediated allergy. (See ["Allergy to penicillins", section on 'Clinical manifestations and incidence'.](#))

Such patients can simply be given the cephalosporin normally, provided the penicillin and cephalosporin in question do not share identical side chains.

- The patient is at greater risk for reacting to a cephalosporin if the reaction to penicillin occurred within the past 10 years, and/or if the symptoms involved were consistent with an IgE-mediated reaction. Such patients may be given a cephalosporin (with a dissimilar side chain) via graded challenge. (See ['Graded challenge'](#) below.)
- Patients whose penicillin reactions were consistent with anaphylaxis are at highest risk and should be desensitized to the required cephalosporin.

Graded challenge — The starting dose for a graded challenge is usually 1/100 or 1/10 of the full dose. Ten-fold increasing doses are administered every 30 to 60 minutes until the full therapeutic dose is reached. An example of a graded challenge to [cefuroxime](#) would be 2.5 mg, 25 mg, and 250 mg given at 60 minute intervals. The safe performance of graded challenges is reviewed in more detail elsewhere. (See ["Allergy to penicillins", section on 'Graded challenge \(test dosing\)'](#).)

Patients selectively allergic to amoxicillin or ampicillin — Patients confirmed to be selectively allergic to [amoxicillin](#) or [ampicillin](#) (ie, who tolerate penicillin) should avoid cephalosporins with identical R-group side chains ([table 1](#)) or receive them via desensitization. They may receive cephalosporins with dissimilar side chains normally. Selective allergy to amoxicillin or ampicillin can only be determined with certainty with skin testing. (See ["Allergy to penicillins", section on 'Allergens'](#) and ["Allergy to penicillins", section on 'Desensitization'](#).)

This approach is based upon a small number of reports that evaluated patients proven to be selectively allergic to [amoxicillin](#) or [ampicillin](#) and tolerant to penicillin (via skin testing, in vitro testing, or oral challenge), with challenge to [cefadroxil](#) or [cephalexin](#), respectively ([table 4](#)). Overall, 11/45, or 24 percent reacted to a cephalosporin with identical R-group side chains [[4-6](#)]. Thus, based upon limited data from Spain, the rates of cross-sensitivity between agents with identical side chains appears to be significant among patients selectively allergic to aminopenicillins.

The data regarding clinical cross-reactivity among drugs with similar (but not identical) side chains are even more sparse. Some investigators have proposed that patients who have reacted to a drug with a specific R group avoid all agents with similar R groups [[29](#)], although there are no clinical data regarding cross-sensitivity upon which to base this recommendation.

The management of patients who report a reaction to [amoxicillin](#) or [ampicillin](#) but have NOT been skin tested to determine if they are selectively allergic to the aminopenicillin is based upon clinical risk assessment, as follows:

- Only 10 to 15 percent of patients with a history of penicillin reactions are actually allergic to penicillin.
- Studies of penicillin-allergic patients in the United States and Europe have demonstrated geographical differences in the allergens to which patients become sensitized. These studies are reviewed elsewhere. (See ["Allergy to penicillins", section on 'Allergens'.](#))

In the United States, less than 0.5 percent of penicillin-allergic patients are sensitized to R group side chains (ie, selectively allergic to aminopenicillins). Thus, these patients have a very small chance of reacting to cephalosporins based on side chain similarity. Therefore, they may be approached in identical fashion as described above for penicillin allergy. (See ['Penicillin skin testing is not available'](#) above.)

In southern European populations, up to one-third of [amoxicillin](#)-allergic patients are sensitized to R group side chains. If a cephalosporin with an identical side chain is required, desensitization or cautious graded challenge is indicated. These patients may receive cephalosporins with dissimilar side chains according to the approach described above. (See ['Penicillin skin testing is not available'](#) above.)

CARBAPENEMS — Carbapenems share a common beta-lactam ring with penicillins and hence the potential for allergic cross-reactivity ([figure 1](#)).

Skin test cross-reactivity between these two groups of drugs was evaluated in one study, although patients were not subsequently challenged to confirm clinical reactivity, and skin testing to carbapenems has not been validated [[30](#)]. In this study, 40 patients with a history of penicillin allergy were skin tested to both penicillin and imipenem determinants [[30](#)]. Twenty were skin test-positive to penicillin, and 10 of these individuals also had positive skin tests to imipenem. In contrast, all 20 penicillin skin test-negative patients were also negative to testing with imipenem. This 50 percent skin test cross-reactivity is similar to that found with penicillins and cephalosporins [[8,11](#)]. Similar to the situation with cephalosporins, this does not appear to translate into clinical cross-reactivity.

Clinical cross reactivity between penicillin and carbapenems was studied with retrospective series of hospitalized patients with a history of penicillin allergy treated with imipenem or [meropenem](#). Some but not all of these reports showed somewhat increased rates of reactions to carbapenems compared to patients without a history of penicillin allergy [[31-35](#)]. However, none of these patients underwent diagnostic testing for penicillin allergy to confirm they were allergic to penicillin at time of treatment with carbapenems.

Several subsequent studies confirmed penicillin sensitization with skin testing, and then performed carbapenem challenges [36-39]. These studies demonstrated that 99 percent of patients with positive skin tests to penicillin will tolerate a carbapenem, essentially ruling out IgE-mediated allergic cross-reactivity between the drugs. Collectively, over 500 penicillin skin test-positive adults and children underwent skin testing with imipenem or [meropenem](#), were found to be negative, and then tolerated a graded challenge with the respective carbapenem [36-39]. A small number of penicillin skin test-positive patients (1 percent of the total group) had positive skin tests to carbapenem and so were not challenged with it [36-38].

Based on these data, clinical cross-reactivity between penicillins and carbapenems appears to be much lower than would be expected from skin test data. Hence the approach to patients with a history of penicillin allergy who require treatment with carbapenems is analogous to what was described above for cephalosporins:

- If penicillin skin testing is available and is negative, patients may safely receive carbapenems.
- If penicillin skin testing is positive, carbapenem may be administered via a 2 or 3 step graded challenge.
- If penicillin skin testing is unavailable, carbapenems may also be administered via graded challenge. This is based on the fact that only 10 to 15 percent of individuals with a history of penicillin allergy are actually allergic, and of those, over 99 percent are able to tolerate carbapenems.

MONOBACTAMS (AZTREONAM) — [Aztreonam](#) is the only clinically available monobactam and it has a monocyclic beta-lactam structure ([figure 1](#)). In vitro studies and skin testing studies demonstrated no immunologic cross-reactivity between penicillin and aztreonam [40,41]. Likewise, aztreonam challenges of penicillin skin test-positive patients revealed no reactions [42-44]. Based on this evidence, patients with a history of penicillin allergy may safely receive aztreonam.

INFORMATION FOR PATIENTS — Educational materials on this topic are available for patients. (See "[Patient information: Allergy to penicillin and related antibiotics](#)".) We encourage you to print or e-mail this topic review, or to refer patients to our public web site, www.uptodate.com/patients, which includes this and other topics.

SUMMARY AND RECOMMENDATIONS — Penicillin-allergic patients can often be safely treated with other beta-lactam drugs. This requires an understanding of what is known from the literature about cross reactivity patterns among different beta-lactams, as well as the ability to assess an individual patient's risk.

- Among all patients reporting penicillin allergy, 85 to 90 percent will tolerate a penicillin, either because they were never allergic or because they had an earlier allergy that subsequently resolved. (See ["Allergy to penicillins"](#).)
- Past studies of cross-reactivity among beta-lactam antibiotics often overestimated the risk because immunologic evidence of cross-reactivity of IgE antibodies in skin tests and in vitro assays does not always translate into clinical cross-sensitivity with actual treatment. Patients with multiple drug allergy syndrome are another important source of confounding in cross-reactivity studies. (See ["Introduction"](#) above.)
- Among penicillin skin-test positive patients, approximately 2 percent will react to a cephalosporin. (See ["Risk of administration in patients with confirmed penicillin allergy"](#) above.)
- The risk of a penicillin-allergic patient reacting to a cephalosporin may be assessed based upon the results of penicillin skin testing (if available), the clinical features of the penicillin reaction, and the time elapsed since the last reaction to penicillin ([algorithm 1](#)). (See ["Algorithm for management"](#) above.)
- Patients who reacted initially to [amoxicillin](#) or [ampicillin](#) should undergo the same risk assessment as penicillin-allergic patients. In addition, they should avoid cephalosporins with identical R-group side chains if they have positive skin tests to aminopenicillins, OR receive these cephalosporins via graded challenge or desensitization ([table 1](#)). (See ["Patients selectively allergic to amoxicillin or ampicillin"](#) above.)
- More than 99 percent of penicillin skin test-positive patients tolerate treatment with carbapenems, despite a significant rate of cross-reactivity between penicillins and carbapenems on skin testing.
- An individual patient's risk of reacting to a carbapenem may be assessed based upon the results of penicillin skin testing, the clinical features of the penicillin reaction, and the time elapsed since the last reaction to penicillin. The approach is identical to that for cephalosporins. (See ["Carbapenems"](#) above.)
- [Aztreonam](#) is the only monobactam currently available for clinical use. There is no evidence of immunologic cross reactivity between penicillins and monobactams, and penicillin-allergic patients may receive [aztreonam](#) normally. (See ["Monobactams \(aztreonam\)"](#) above.)

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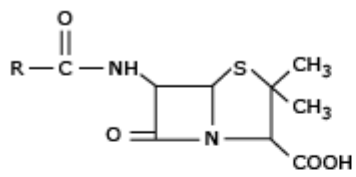
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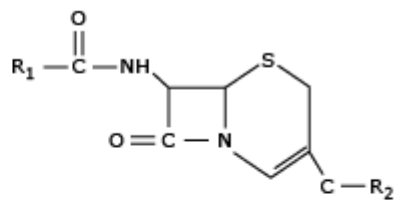
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GRAPHICS

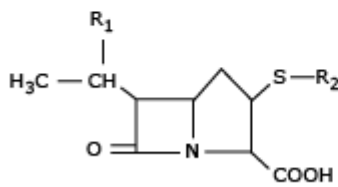
Structure of penicillins and related drugs



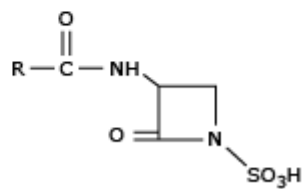
Penicillins



Cephalosporins



Carbapenems



Monobactams

Cephalosporins and penicillins with common side chains

Amoxicillin	Ampicillin
Cefadroxil	Cefaclor
Cefprozil	Cephalexin
Cefatrizine	Cephradine
	Cephaloglycin
	Loracarbef (carbacephem)

List of cephalosporins that share identical R1-group side chains with R-group side chain of amoxicillin and ampicillin.

Results of cephalosporin challenges in patients with histories of penicillin allergy

Reference	Cephalosporin reaction rate		Cephalosporins administered
	History of pcn allergy (percent)	No history of pcn allergy (percent)	
Dash CH	25/324 (7.7)	140/17,216 (0.8)	Cephalexin and cephaloridine
Petz LD	57/701 (8.1)	285/15,007 (1.9)	Cephalexin, cephaloridine, cephalothin, cefazolin and cefamandole
Goodman EJ	1/300 (0.3)	1/2431 (0.04)	Cefazolin (in all but one patient)
Daulat SB	1/606 (0.17)	15/22,664 (0.07)	1st generation (42 percent)
			2nd generation (21 percent)
			3rd/4th generations (37 percent)
Fonacier L	7/83 (8.4)	Not reported	1st generation (59 percent)
			2nd generation (8.4 percent)
			3rd generation (25 percent)
			4th generation (7 percent)

Summary of studies of cephalosporin challenges in patients with a history of penicillin (pcn) allergy without preceding penicillin allergy testing.

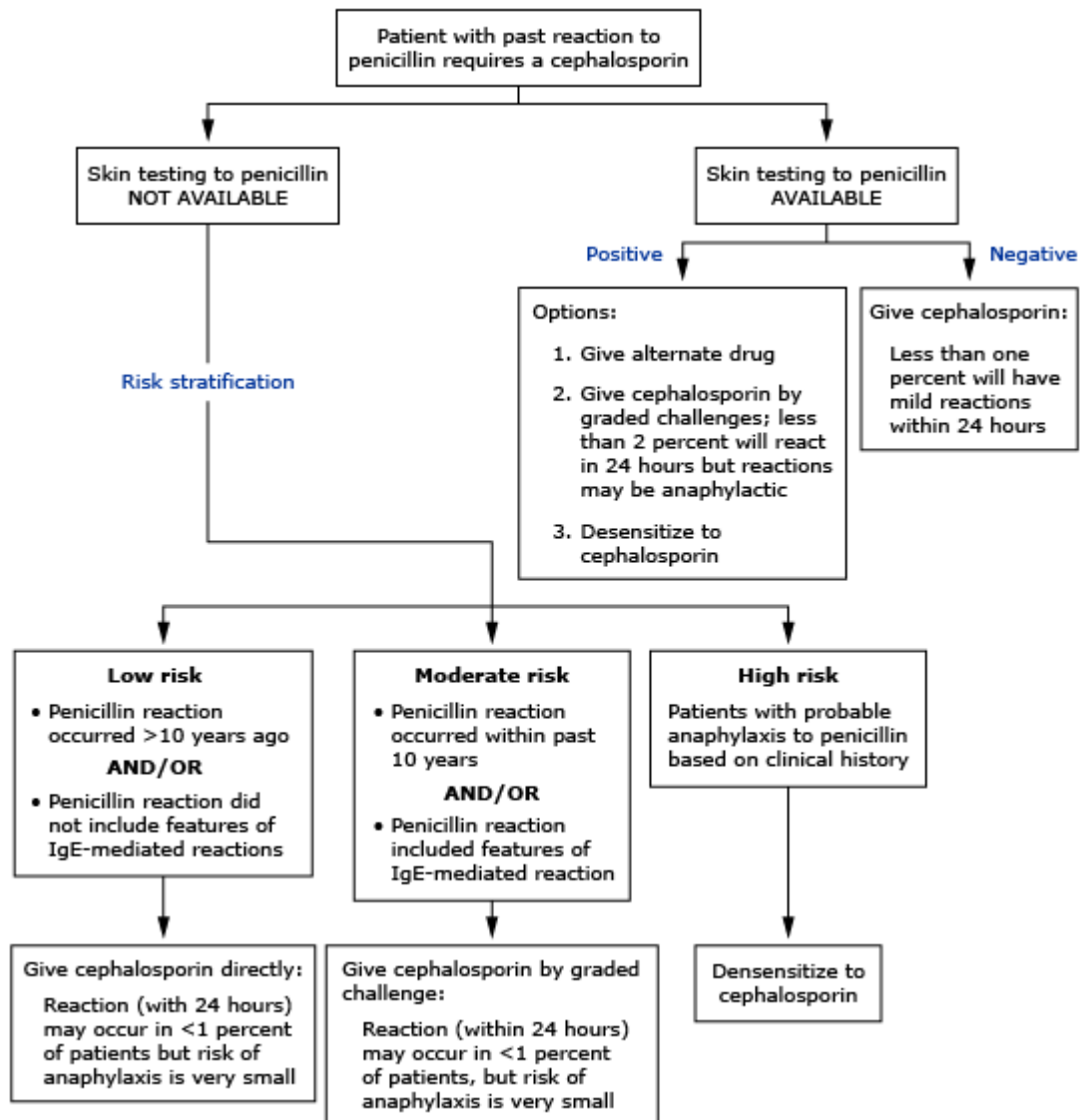
Use of cephalosporins in patients with positive skin tests to penicillin

Reference	Number of patients	Number of reactions (percent)	Cephalosporin skin testing	Comment
Girard JP (1968)	23	2 (8.7)	No	Both reactions to cephaloridine
Assem ESK (1974)	3	3 (100)	No	All reactions to cephaloridine
Warrington RJ (1978)	3	0	Yes	
Solley GO (1982)	27	0	No	
Saxon A (1987)	62	1 (1.6)	No	Cephalosporin not noted
Blanca M (1989)	16	2 (12.5)	No	Both reactions to cefamandole
Shepherd GM (1993)	9	0	No	
Audicana M (1994)	12	0	Yes	
Pichichero ME (1998)	39	2 (5.1)	No	Reaction to cefaclor and ?
Novalbos A (2001)	23	0	Yes	
Macy E (2002)	42	1 (2.4)	No	Reaction to cefixime
Romano A (2004)	75	0	Yes	
Greenberger PA (2005)	6	0	No	

Park MA (2006)	37	2 (5.4)	No	Cephalosporins not noted
Total	377	13 (3.4)		

Summary of penicillin skin test-positive patients challenged with cephalosporins, excluding patients selectively allergic to amoxicillin or ampicillin (skin test positive to semisynthetic penicillin but negative to major and minor penicillin determinants).

Administration of a cephalosporin to a patient with a history of penicillin allergy



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Cross reactivity between penicillins and cephalosporins with common side chains

Reference	Selective allergy to	Cephalosporin with identical side chain	Reaction rate (percent)
Audicana (1994)	Ampicillin	Cephalexin	1/10 (10)
Sastre J (1996)	Amoxicillin	Cefadroxil	2/16 (12)
Miranda A (1996)	Amoxicillin	Cefadroxil	8/21 (38)
Total			11/47 (23)

Summary of patients proven to be selectively allergic to amoxicillin or ampicillin challenged with cephalosporins that contain identical R-group side chains.

